Studies in Protoberberine Alkaloids. Part 12.[1] Novel Transformation of some 1-(2-Bromo-α-methylbenzyl)-1,2,3,4-tetrahydroisoquinolines to Isoquinobenzoxazepines During Mannich Reactions

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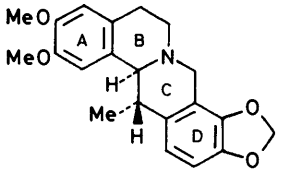
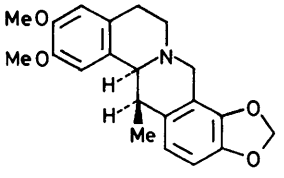
1-(2-Bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7a) and its analogues (26a) and (26b) were prepared by well known routes. When they were treated with formaldehyde and hydrochloric acid the expected Mannich reaction to give the 12-bromo-13-methyltetrahydroprotoberberines did not take place. A novel rearrangement occurred to give the unexpected isoquinobenzoxazepines (16a), (27a), and (27b), respectively, the structures of which were assigned by i.r., u.v., n.m.r., and mass spectroscopy and confirmed by comparison of some of their degradation products with compounds synthesised by standard methods. Unequivocal evidence for the structure and stereochemistry of these compounds were obtained by an *X*-ray crystallographic study on compound (27a). Some aspects of the scope and mechanism of this novel reaction have been explored.

THALICTRIFOLINE [2] and base II (cavidine) [3] are stereoisomeric 13-methyltetrahydroprotoberberine alkaloids with structures (1) and (2), respectively. Since it is the



(1)



(2)

only naturally occurring 13-methyltetrahydroprotoberberine with the B–C rings having the *cis*-quinolizidine conformation,[4] the synthesis of thalictrifoline is an interesting problem. Assignment of its absolute configuration is even more challenging because the use of o.r.d. data is precluded in this case.[4] A synthesis with starting compounds of known chirality would be a logical approach to this problem. As an extension of our interest in the chemistry of protoberberines [5] and also to solve this problem we attempted to synthesise (±)-thalictrifoline and (±)-base II by the route in Scheme 1. If this route had proved to be successful the synthesis would have been repeated with optically active acid (3).

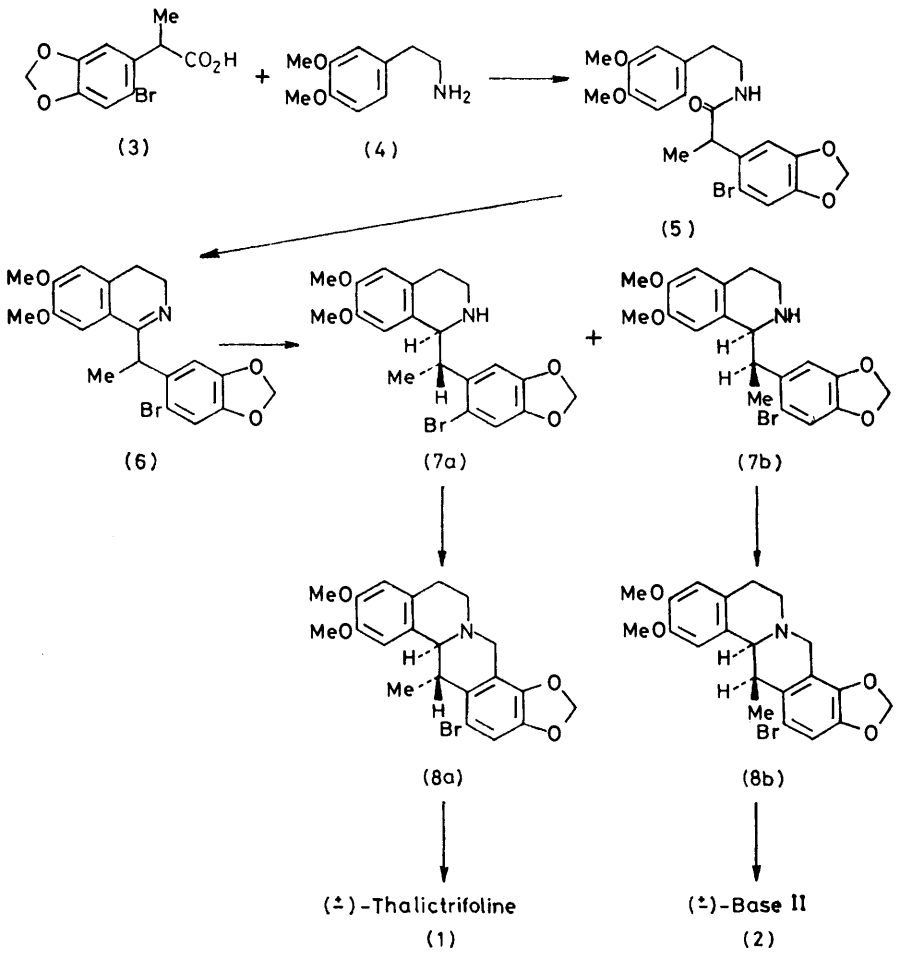
The synthesis in Scheme 1 is based on an adaptation of the Shamma *et al.* [6] synthesis of 13-methyltetrahydro-ψ-protoberberines with one modification, *viz.*, use of bromine as a blocking group to force the Mannich cyclisation in the desired direction to form the required 9,10-oxygenated products. Though we were unable to synthesise thalictrifoline by this method, we have observed some unexpected and hitherto unencountered results in the Mannich cyclisation; [7] we report now full details of these observations, together with results relating to the scope, mechanism, and stereospecificity–stereoselectivity of this novel reaction.

2-(3,4-Methylenedioxyphenyl)propionic acid [6] was brominated in acetic acid to the bromo-acid (3). Condensation of the acid chloride of (3) with homoveratrylamine (4) led to the amide (5) which was smoothly cyclised to the dihydroisoquinoline (6) using phosphorus trichloride oxide. Sodium borohydride in methanol reduced the dihydro-base (6) to the tetrahydro-comround (7a) exclusively. The *erythro* stereochemistry for (7a) was assigned on the basis of the chemical shift of the *C*-methyl group in the n.m.r. spectrum (δ 1.23). More particularly, the debromo-derivative obtained by catalytic hydrogenation of (7a) showed the methyl doublet at δ 1.41; in similar molecules Shamma and his co-workers [8] reported chemical shifts of δ 0.96 and 1.41 respectively for the *threo*- and *erythro*-isomers.

The tetrahydroisoquinoline (7a) did not lead to the expected 12-bromotetrahydroprotoberberine (8a) when treated with formaldehyde and acid under a variety of conditions. In all cases we obtained (70—85% yield) a product with m.p. 210 °C. This product, compound (A) ($C_{21}H_{23}NO_5$, M^+, m/e 369) was obviously not the expected tetrahydroprotoberberine (8a). Its ^{1}H n.m.r. spectrum ($CDCl_3$) showed signals due to two methoxy-groups [δ 3.80 (s, 3 H) and 3.88 (s, 3 H)], a methylenedioxy group [δ 5.95 (s, 2 H)], and a doublet due to the *C*-methyl group [δ 1.65 (d, *J* 6.5 Hz, 3 H)]. Four aromatic protons were observed as three singlets at δ 6.55 (1 H), 6.75 (2 H), and 6.82 (1 H). A four-proton multiplet at δ 2.75 indicated the presence of two methylene units adjacent to each other as in the case of the C-3 and C-4 methylene groups of a 1,2,3,4-tetrahydroisoquinoline unit. A quartet at δ 5.20 (1 H, *J* 7.5 Hz) could be assigned to the methine proton of the C*H*Me unit. In addition to these signals a pair of doublets (*J* 15 Hz) at δ 3.88 (1 H) and 4.71 (1 H) were observed which could be due to the CH_2 group introduced by formaldehyde. The n.m.r. spectrum in trifluoroacetic acid exhibited the following signals: δ 1.75 (3 H, d, CH*Me*), 3.34 (2 H, t, $ArCH_2$), 4.02 (3 H, s, OMe), 4.12 (3 H, s, OMe), 4.29 (2 H, t, NCH_2), 6.10 (2 H, s, OCH_2O), and 6.92, 7.07, 7.14, and 7.27 (4 H, ArH). Other signals were observed at δ 5.19br (2 H, s) and 8.50br (1 H, s). The signals at δ 3.34, 4.29, and 8.50 are reminiscent of the 4-, 3-, and 1-H signals, respectively, for 1-unsubstituted 3,4-dihydroisoquinolines.

The u.v. spectra of compound (A) provided more

evidence for its structure: $\lambda_{max.}$(EtOH) 247, 290, 312, and 368 nm (log ε 4.23, 3.86, 3.57, and 3.54); $\lambda_{max.}$(EtOH + HCl) 247, 311, and 365 nm (log ε 4.34, 4.05, and 4.03); $\lambda_{max.}$(EtOH + NaOH) 230 (sh) and 285 nm (log ε 4.03 and 3.86); $\lambda_{max.}$($CHCl_3$) 288 nm (log ε 3.88); $\lambda_{max.}$($CHCl_3$ + HCl) 292, 312, and 366 nm (log ε 3.91, 3.95, and 3.99). All alkoxy-*N*-benzyl-3,4-dihydroisoquinolinium salts exhibit u.v. maxima around 310 and 360 nm which upon addition of alkali shift to a single absorption maximum at 290 nm which is characteristic of a tetrahydroisoquinoline. The u.v. data of compound (A) therefore suggested the presence of an *N*-substituted 3,4-dihydroisoquinolinium chromophore.



SCHEME 1 Attempted unsuccessful synthesis of (1) and (2)

Compound [a]	λ_{max}(EtOH)/nm (log ε)	λ_{max}(EtOH + NaOH)/nm (log ε)
(9)	245, 308, 360 (4.15, 3.88, 3.80)	230, 277, 308 (4.34, 3.79, 3.73)
(10)	210 (sh), 247, 308, 360 (4.37, 4.31, 4.06, 4.06)	282 (3.60)
(11)	250, 312, 365 (4.30, 4.08, 4.08)	282 (3.62)
(12)	248, 312, 367 (4.34, 4.08, 4.08)	284 (3.93)
(13)	250, 313, 365 (4.37, 4.08, 4.05)	282 (3.75)
(14)	233, 285 (3.99, 3.85)	

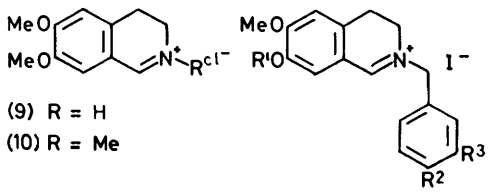
[a] Compounds (9)—(14) are all known. Some of them were readily available to us and others were prepared according to classical methods.

To confirm this, the u.v. spectra of model compounds were recorded (Table). In ethanol solution compounds (9)—(14) all exhibited maxima around 310 and 360 nm, but on addition of alkali the spectrum of compound (9) changed to that of a 3,4-dihydroisoquinoline with maxima at 230, 277, and 308 nm while compounds (10)—(13) showed a single maximum around 282—285 nm. These data suggested that compound (A) possibly included the chromophore (15a) which in polar solvents existed in equilibrium with the dihydroisoquinolinium species (15b).

Further evidence for the structure of compound (A) was obtained from degradation studies. With sodium borohydride in methanol or on catalytic hydrogenation in the presence of Adams catalyst compound (A) was reduced to a dihydro-derivative (B) ($C_{21}H_{25}NO_5$, M^+, *m/e* 371).* I.r. bands at 3 175 (OH) and 1 120 cm^{-1} (CO stretching) indicated the presence of a hydroxy-

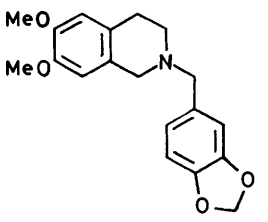
* This dihydro-derivative was also obtained as a minor product in the Mannich reaction with (7a), presumably by reduction of (A) by HCHO.

group in compound (B). Its u.v. spectrum [$\lambda_{max.}$(EtOH) 230 (sh) and 288 nm (log ε 4.21 and 3.89)] closely resembled that of (14), and its n.m.r. spectrum ($CDCl_3$)



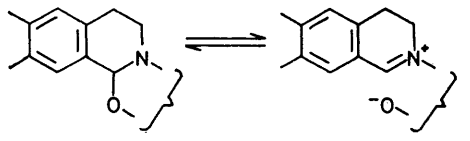
(9) R = H
(10) R = Me

(11) R^1 = Me ; R^2 = R^3 = H
(12) R^1 = Me ; R^2 + R^3 = OCH_2O
(13) R^1 = CH_2Ph ; R^2 = OCH_2Ph ; R^3=H



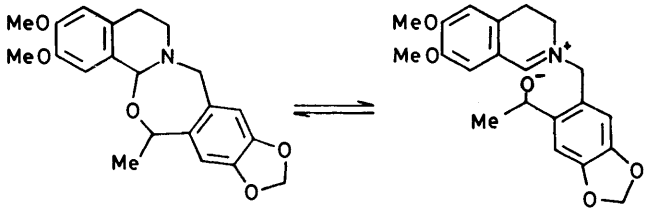
(14)

showed the following signals: δ 1.53 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.80br (4 H, s), 3.30 (1 H, d, *J* 12.5 Hz),

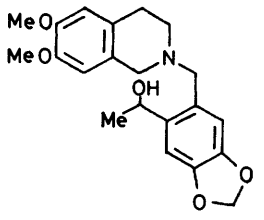


(15a) (15b)

3.80 (6 H, s, 2 × OMe), 4.10 (1 H, d, *J* 12.5 Hz), 5.00 (1 H, q, *J* 6.5 Hz), 5.05 (2 H, s, OCH_2O), 6.45 (1 H, s), 6.55 (1 H, s), 6.75 (1 H, s), and 6.95 (1 H, s).



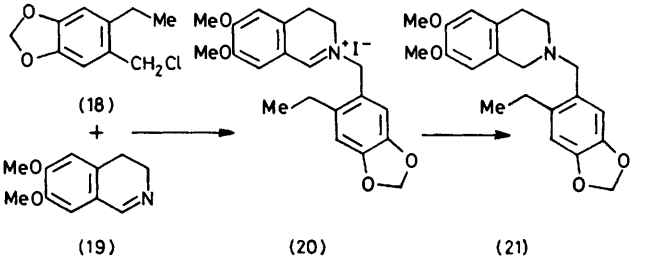
(16a) (16b)



(17)

Compound (B) readily formed a monoacetate, m.p. 144 °C, in the n.m.r. spectrum of which the quartet due to the C*H*Me proton was shifted downfield by 1.22 p.p.m. compared to its position for compound (B), indicating that the acetoxy-group was attached to the carbon bearing the methyl group. Taking all the foregoing evidence into consideration it was thought that the most likely structure for compound (A) was that in which an oxygen atom was included between C-13 and C-13a of the tetrahydroprotoberberine system, *i.e.* structure (16a). The dihydro-derivative (B) accordingly must have the structure (17). Assignment of structure (16a) to the compound (A) was substantiated by the following experiments. Compound (B) was catalytically hydrogenated (Pd–C; aq. HCl) yielding a deoxy-compound, m.p. 113—115 °C, which was identified as (21) by comparison with a sample synthesised by the route in Scheme 2. 3,4-Dihydro-6,7-dimethoxyisoquinoline (19) was alkylated with 2-ethyl-4,5-methylenedioxybenzyl chloride (18) in the presence of potassium iodide and the resulting quaternary iodide (20) was reduced with sodium borohydride in methanol to afford (21) (identity by t.l.c., n.m.r., i.r., and mass spectra).

The isoquinobenzoxazepine structure (16a) for compound (A) is in accordance with all its spectral and degradation data. Its u.v. spectrum in ethanol indicates that compound (A) exists in equilibrium with species



(18) + (19) (20) (21)

SCHEME 2

(16b) (or its protonated form), the latter in preponderance. The equilibrium is completely shifted towards the form (16a) by the addition of alkali to solutions in ethanol and aprotic solvents like chloroform and to the protonated form (16b) in acids. The n.m.r. spectra in $CDCl_3$ and CF_3CO_2H would likewise correspond to structures (16a) and the protonated form (16b), respectively. A possible mechanism for the formation of the anomalous compound is given in Scheme 3.

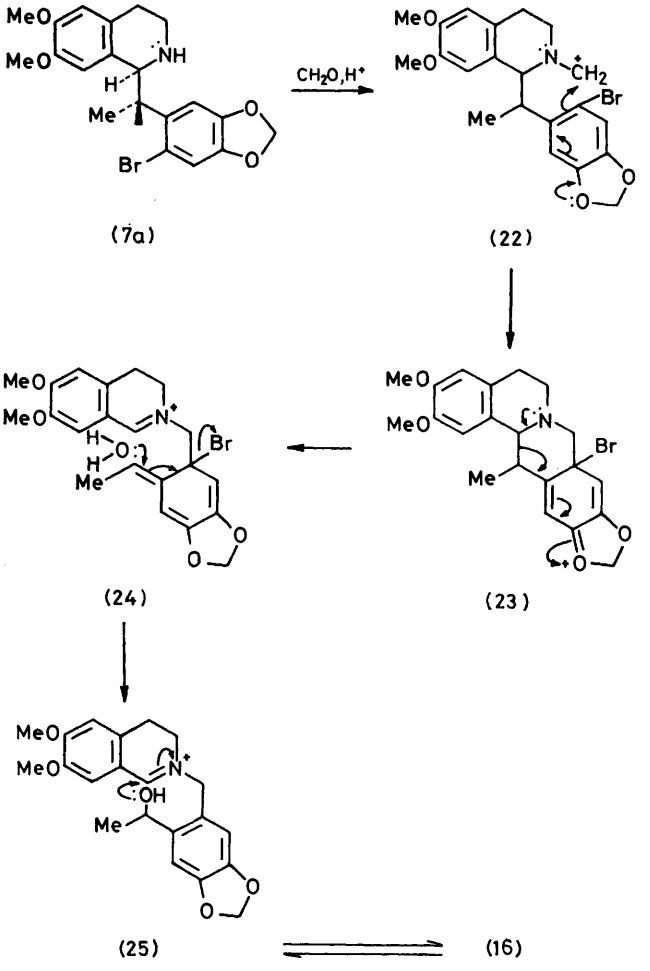
The reaction was extended to compounds (26a) and (26b) which were prepared in a manner analogous to (7a). On treatment with formaldehyde and acid (26a) and (26b) led to the anomalous products (27a) and (27b), respectively, which are analogous to (16a), indicating the general nature of the rearrangement. The i.r., u.v., n.m.r., and mass spectra of (27a) and (27b) were similar to those of (16a). Compound (27a) was transformed to a dihydrodeoxy-derivative [analogous to (21)] whose structure was confirmed by synthesis.

Compound (27a) formed prisms from ethyl acetate–hexane suitable for *X*-ray crystallographic studies necessary to confirm the gross structure and establish the stereochemistry.* These studies [7] confirmed the

* Dreiding models of (16a) indicated great flexibility of rings B and C which precluded use of tools like n.m.r. spectroscopy for deduction of stereochemistry.

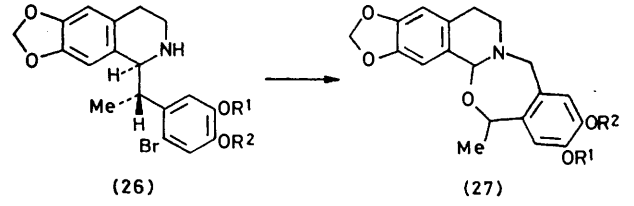
proposed isoquinobenzoxazepine structure for the anomalous compound and showed that 13- and 14a-H and the lone pair on nitrogen were all *cis* as shown in (28).

Our attempts to prepare (7b), the diastereoisomer of (7a), from (6) yielded only (7a) and/or dehalogenated products. Hence the question as to whether (7b) would undergo the abnormal Mannich reaction, and if so, with what stereochemical consequence, remains unanswered. We also wished to study the reaction with an optically active substrate. Compound (26a) was converted into



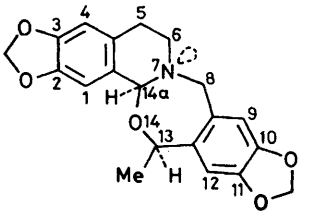
SCHEME 3

its acid salt with (—)-di-*O*-*p*-toluoyltartaric acid and the product crystallised to constant rotation to afford a



a; $R^1,R^2 = CH_2$
b; $R^1 = R^2 = Me$

homogenous salt, $[\alpha]_D$ —40°. The base liberated from this salt was a gum which could not be crystallised, unlike racemic (26a), m.p. 127°. The resolved base had no rotation at sodium D line, but o.r.d. measurements



established it to be active: $[\phi]_{306}$ +3 716°; $[\phi]_{283}$ —4 605°; $[\phi]_{279}$ —4 363°; $[\phi]_{275}$ —4 646°; $[\phi]_{251}$ —9 292°; $[\phi]_{232}$ +14 261° (*c*, 1.495, MeOH, 25°). Reaction of the resolved base with formaldehyde under Mannich conditions led to the formation of racemic (27a) thus showing that the reaction is not stereospecific or even stereoselective.

EXPERIMENTAL

M.p.s are uncorrected. U.v. spectra were recorded with a Beckman DK2A spectrophotometer for solutions in aqueous ethanol (95%) unless otherwise stated. I.r. spectra were recorded with Perkin-Elmer Infracord and model 421 IR spectrophotometers. ^1H N.m.r. spectra were recorded with a Varian A60 spectrometer, with tetramethylsilane as internal reference. Mass spectra were recorded with Varian Mat CH7 mass spectrometer and o.r.d. measurements with a Jasco J-20 spectropolarimeter.

2-(2-*Bromo*-4,5-*methylenedioxyphenyl*)*propionic Acid* (3).—Sodium acetate (9.5 g) was added to a solution of 2-(3,4-methylenedioxyphenyl)propionic acid [6] (9.5 g) in glacial acetic acid (150 ml), and bromine (3 ml) in glacial acetic acid (36 ml) was added dropwise to the stirred solution. The solution was then stirred for 2 h and filtered, and the filtrate was washed with cold water, dried, and crystallised from chloroform to yield the *bromo acid* (3) (8.2 g), m.p. 157° (Found: C, 43.7; H, 3.7. $C_{10}H_9BrO_4$ requires C, 43.95; H, 3.3%).

2-(2-*Bromo*-4,5-*dimethoxyphenyl*)*propionic Acid*.—A solution of 2-(3,4-dimethoxyphenyl)propionic acid (9.3 g), prepared by the alkaline hydrolysis of methyl 2-(3,4-dimethoxyphenyl)propionate,[8] in glacial acetic acid (150 ml) was stirred with sodium acetate (9.3 g) at room temperature, and bromine (3 ml) in glacial acetic acid (36 ml) was added. The solution was then stirred for 2 h, water (150 ml) was added, and the precipitate was filtered off and washed with water. The solid was dried and crystallised from ethyl acetate to yield the *bromo acid* (7.89 g), m.p. 105° (Found: C, 46.3; H, 4.9. $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.5%).

2-(2-*Bromo*-4,5-*methylenedioxyphenyl*)-N-(3,4-*dimethoxyphenethyl*)*propionamide* (5).—A mixture of the bromo-acid (3) (27.3 g), freshly distilled thionyl chloride (13.5 ml), dry benzene (200 ml), and pyridine (1 ml) was heated under reflux on a steam-bath for 2 h. Excess of reagents and solvent were removed *in vacuo*. The residue, the acid chloride of (3), was washed with benzene and dissolved in dry chloroform (50 ml), and this solution was added to a vigorously stirred suspension of homoveratrylamine (4) (20 g) in chloroform (200 ml), sodium carbonate (28 g), and water (120 ml) at 0°. The mixture was then stirred for 2 h and the chloroform layer was washed with water, dilute

hydrochloric acid (5%), and again with water, and dried (Na_2SO_4). Evaporation left a solid which was crystallised from benzene to yield the *amide* (5) (45 g), m.p. 140°, $\nu_{max.}$(KBr) 1 640 (C=O) and 3 295 (NH) cm^{-1} (Found: C, 55.2; H, 5.35; N, 3.4. $C_{20}H_{22}BrNO_5$ requires C, 55.0; H, 5.05; N, 3.2%).

Similarly were prepared 2-(2-*bromo*-4,5-*methylenedioxyphenyl*)-N-(3,4-*methylenedioxyphenethyl*)*propionamide*, m.p. 134°, $\nu_{max.}$(KBr) 1 640 (C=O) and 3 400 (NH) cm^{-1} (Found: C, 54.6; H, 4.6; N, 3.4. $C_{19}H_{18}BrNO_5$ requires C, 54.3; H, 4.3; N, 3.3%) and 2-(2-*bromo*-4,5-*dimethoxyphenyl*)-N-(3,4-*methylenedioxyphenethyl*)*propionamide*, m.p. 97°, $\nu_{max.}$ (KBr) 1 640 (C=O) and 3 300 (NH) cm^{-1} (Found: C, 55.2; H, 5.3; N, 2.95. $C_{20}H_{22}BrNO_5$ requires C, 55.0; H, 5.0; N, 3.2%).

1-(2-*Bromo*-α-*methyl*-4,5-*methylenedioxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (6).—A mixture of the amide (5) (10 g), freshly distilled phosphorus trichloride oxide (20 ml), and dry toluene (70 ml) was heated under reflux for 2 h on an oil-bath. The mixture was cooled, diluted with dry hexane (100 ml), and left for 30 min at room temperature. The supernatant layer was decanted off. Dry hexane (100 ml) was again added to the residue, which was set aside for 30 min and decanted as before. A solution of the oily residue in chloroform was basified with ammonium hydroxide, and the chloroform layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallised from ethanol to give the *dihydroisoquinoline* (6) (8 g), m.p. 148°, $\lambda_{max.}$(EtOH) 230, 282, and 305 nm (log ε 4.37, 3.94, and 3.95); δ($CDCl_3$) 1.43 (3 H, d, *J* 7 Hz, CH*Me*), 2.63 (2 H, t, *J* 7 Hz, CH_2), 3.78 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.63 (1 H, q, *J* 7 Hz, C*H*Me), 5.83 (2 H, s, OCH_2O), and 6.62, 6.68, 6.90, and 7.00 (4 H, 4s, ArH) (Found: C, 57.6; H, 5.2; N, 3.5. $C_{20}H_{20}BrNO_4$ requires C, 57.4; H, 4.8; N, 3.35%).

1-(2-*Bromo*-α-*methyl*-4,5-*methylenedioxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline*.— 2-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-(3,4-methylenedioxyphenethyl)-propionamide was cyclised, as just described, to the *dihydroisoquinoline* which was crystallised from ethanol, m.p. 191°, $\lambda_{max.}$(EtOH) 229, 290, and 310 nm (log ε 4.39, 3.88, and 3.86); δ($CDCl_3$) 1.42 (3 H, d, *J* 7 Hz, CH*Me*), 2.60 (2 H, t, *J* 7 Hz, CH_2), 3.73 (2 H, m, CH_2), 4.63 (1 H, q, *J* 7 Hz, C*H*Me), 5.86 and 5.87 (4 H, each s, 2 × OCH_2O), and 6.60—7.05 (4 H, ArH) (Found: C, 56.8; H, 4.3; N, 3.3. $C_{19}H_{16}BrNO_4$ requires C, 56.7; H, 4.0; N, 3.5%).

1-(2-*Bromo*-α-*methyl*-4,5-*dimethoxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline*.— 2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(3,4-methylenedioxyphenethyl)propionamide was cyclised, as just described, to the *dihydroisoquinoline* which was crystallised from benzene–light petroleum (b.p. 40—60°), m.p. 131°, $\lambda_{max.}$(EtOH) 281 and 313 nm (log ε 4.06 and 4.04); δ($CDCl_3$) 1.43 (3 H, d, *J* 7 Hz, CH*Me*), 2.60 (2 H, t, CH_2), 3.72 (3 H, s, OMe), 3.83 (3 H, s, OMe), 4.61 (1 H, q, C*H*Me), 5.87 (2 H, s, OCH_2O), and 6.62, 6.74, 6.92, and 7.05 (4 H, each s, ArH) (Found: C, 57.4; H, 5.1; N, 3.1. $C_{20}H_{20}BrNO_4$ requires C, 57.4; H, 4.8; N, 3.3%).

1-(2-*Bromo*-α-*methyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (7a).—To a solution of the dimethoxyisoquinoline (6) (5 g) in chloroform (25 ml), methanol (200 ml) was added followed by sodium borohydride (1.2 g) in small portions. The solution was left overnight at room temperature and the solvent was then removed *in vacuo*. The residue was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallised from hexane to yield a single stereoisomer of the *tetrahydroisoquinoline* (7a) (4.2 g), m.p. 157°, $\lambda_{max.}$(EtOH) 231 (sh) and 291 nm (log ε 4.16 and 3.90); δ($CDCl_3$) 1.23 (3 H, d, *J* 7 Hz, CH*Me*), 1.85 (1 H, s, NH), 3.83 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.95 (1 H, q, *J* 7 Hz, C*H*NH), 5.93 (2 H, s, OCH_2O), 6.60 (2 H), 7.00 (1 H), and 7.33 (1 H, ArH) (Found: C, 57.1; H, 5.6; N, 3.7. $C_{20}H_{22}BrNO_4$ requires C, 57.15; H, 5.3; N, 3.4%).

1-(2-*Bromo*-α-*methyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (26a).—The corresponding dihydroisoquinoline, prepared as already described, was reduced with sodium borohydride in methanol as just described. The *tetrahydroisoquinoline* (26a) was crystallised from hexane, m.p. 127°; $\lambda_{max.}$(EtOH) 229 (sh) and 287 nm (log ε 3.98 and 3.92); δ($CDCl_3$) 1.20 (3 H, d, *J* 7 Hz, CH*Me*), 1.95 (1 H, s, NH), 4.15 (1 H, d, *J* 7 Hz, C*H*NH), 5.87 and 5.93 (4 H, each s, 2 × OCH_2O), and 6.56, 6.98, and 7.17 (4 H, 3 × s, ArH), *m/e* 404, 402 (M^+, ^{81}Br, ^{79}Br) (Found: C, 57.0; H, 4.9; N, 2.95. $C_{19}H_{18}BrNO_4$ requires C, 56.5; H, 4.5; N, 3.45%).

1-(2-*Bromo*-α-*methyl*-4,5-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (26b).—The corresponding dihydroisoquinoline, prepared as before, was reduced with sodium borohydride in methanol as just described. The tetrahydroisoquinoline was crystallised from ethyl acetate–light petroleum (b.p. 40—60°), m.p. 113°, $\lambda_{max.}$(EtOH) 225 (sh) and 289 nm (log ε 4.14 and 4.02); δ($CDCl_3$) 1.25 (3 H, d, *J* 7 Hz, CH*Me*), 3.83 (6 H, s, 2 × OMe), 5.86 (2 H, s, OCH_2O), and 6.53, 6.56, 7.00, and 7.02 (4 H, 4s, ArH) (Found: C, 57.1; H, 5.3; N, 3.4. $C_{20}H_{22}BrNO_4$ requires C, 57.15; H, 5.38; N, 3.4%).

5,6,7,8,13,14a-*Hexahydro*-2,3-*dimethoxy*-13-*methyl*-10,11-*methylenedioxyisoquino*[1,2-c][2,4]*benzoxazepine* (*Compound* A) (16a).—(a) *Reaction of* (7a) *with formalin and ethanol*. A mixture of the hydrochloride of (7a) (500 mg), ethanol (20 ml), water (15 ml), and formalin (37%; 3 ml) was heated under reflux for 3 h. The solution was concentrated *in vacuo*, cooled, basified with ammonium hydroxide, and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (400 mg) formed needles from ethyl acetate of the *isoquinobenzoxazepine* (16a), m.p. 210°; for u.v., n.m.r., and mass spectral data see Discussion section (Found: C, 68.1; H, 6.5; N, 3.8. $C_{21}H_{23}NO_5$ requires C, 68.3; H, 6.3; N, 3.8%).

(b) *Reaction of* (7a) *with formalin and formic acid*. A mixture of the tetrahydroisoquinoline (7a) (500 mg), water (25 ml), formic acid (3 ml), and formalin (37%; 10 ml) was heated under reflux for 3 h. The mixture was cooled, basified with ammonium hydroxide, and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to give a solid which was shown to contain two products. These were separated by column chromatography over silica-gel using chloroform as eluant. The compound with the higher R_F was crystallised from hexane to yield compound (B) (17) (50 mg), m.p. 151°, and the one with the lower R_F was crystallised from ethyl acetate to yield compound (A) (16a) (350 mg). Compound (B) was identical with the sodium borohydride reduction product of (16a) (see later).

5,6,7,8,13,14a-*Hexahydro*-13-*methyl*-2,3:10,11-*bis*(*methylenedioxy*)*isoquino*[1,2-c][2,4]*benzoxazepine* (27a).—A mixture of the hydrochloride of (26a) (1.32 g), ethanol (60 ml), water (45 ml), and formalin (37%; 10 ml) was heated under

reflux for 3 h. The solution was concentrated under reduced pressure, cooled, basified with ammonium hydroxide, and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to give a solid which was crystallised from ethyl acetate–light petroleum (b.p. 40—60°), to yield the *bismethylenedioxy-compound* (27a) (0.87 g), m.p. 210°; $\lambda_{max.}$(EtOH) 245, 292, 307, and 366 nm (log ε 4.05, 3.92, 3.38, and 3.33); $\lambda_{max.}$(EtOH + NaOH) 290 nm (log ε 3.92); $\lambda_{max.}$(EtOH + HCl) 250, 295, 309, and 365 nm (log ε 4.41, 3.95, 3.96, and 4.08); δ($CDCl_3$) 1.60 (3 H, d, *J* 6 Hz, CH*Me*), 2.65 (4 H, m, CH_2CH_2), 3.86 and 4.72 (each 1 H, d, *J* 15 Hz, C-8-H), 5.18 (1 H, q, *J* 6 Hz, CH*Me*), 5.55 (1 H, s, C-14a-H), 5.87 and 5.95 (4 H, 2s, 2 × OCH_2O), and 6.52, 6.72, and 6.82 (4 H, 3s, ArH); *m/e* 353 (M^+) (Found: C, 68.3; H, 5.7; N, 4.3. $C_{20}H_{19}NO_5$ requires C, 68.0; H, 5.4; N, 4.0%).

5,6,7,8,13,14a-*Hexahydro*-10,11-*dimethoxy*-13-*methyl*-2,3-*methylenedioxyisoquino*[1,2-c][2,4]*benzoxazepine* (27b).—This compound was prepared from the hydrochloride of (26b) as just described, and crystallised from benzene–light petroleum (b.p. 40—60°), m.p. 168—169°; $\lambda_{max.}$(EtOH) 243, 288, 306 (sh), and 366 nm (log ε 4.18, 3.81, 3.50, and 3.59); $\lambda_{max.}$(EtOH + HCl) 248, 293, 308, and 367 nm (log ε 4.33, 3.71, 3.87, and 4.01); $\lambda_{max.}$(EtOH + NaOH) 224 (sh) and 287 nm (log ε 4.02 and 3.98); δ($CDCl_3$) 1.67 (3 H, d, *J* 7 Hz, CH*Me*), 2.74 (4 H, m, CH_2CH_2), 3.91 (3 H, s, OMe), 3.94 and 4.75 (each 1 H, d, *J* 15 Hz, C-8-H), 5.20 (1 H, q, C*H*Me), 5.58 (1 H, s, C-14a-H), 5.90 (2 H, s, OCH_2O), and 6.55, 6.78, 6.83, and 6.89 (4 H, 4s, ArH); *m/e* 369 (M^+) (Found: C, 67.65; H, 6.45; N, 3.9. $C_{21}H_{23}NO_5$ requires C, 68.3; H, 6.3; N, 3.8%).

Degradation of Compound (A) (16a).—(a) *Formation of* N-(2-α-*Hydroxyethyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (17).—(i) *By action of sodium borohydride and methanol on* (16a). To a suspension of the isoquinobenzoxazepine (16a) (400 mg) in methanol (50 ml) was added sodium borohydride (400 mg) in portions. The mixture was left at room temperature for 30 min and the solvent was removed *in vacuo*. The residue was treated with water (50 ml) and extracted with methylene chloride. This extract was washed, dried (Na_2SO_4), and evaporated to leave a gum which was crystallised from hexane to yield the *isoquinoline* (17) (340 mg), m.p. 151°; for spectral data see Discussion section (Found: C, 68.1; H, 6.8; N, 4.2. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.7; N, 3.8%).

(ii) *By action of Adams catalyst on* (16). A solution of (16) (270 mg) in methanol (70 ml) was shaken with hydrogen at 40 lb in^{-2} in a Parr apparatus at room temperature for 3 h in the presence of Adams catalyst (80 mg). The catalyst was then filtered off and the solvent removed *in vacuo*. A brown residue was left which was purified by passing through a short column of silica-gel using chloroform as eluant. Removal of solvent gave a solid which was crystallised from hexane to afford compound (17) (150 mg), m.p. 151°, identical with the product just obtained.

The *acetate* of compound (B) (17) was prepared in the usual way and crystallised from aqueous ethanol as needles, m.p. 144°; δ($CDCl_3$) 1.43 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.98 (3 H, s, OAc), 2.73br (4 H, s), 3.80 and 3.82 (6 H, 2s, 2 × OMe), 5.93 (2 H, s, OCH_2O), 6.22 (1 H, q, *J* 6.5 Hz, –C*H*MeOAc), and 6.47, 6.58, 6.80, and 6.93 (4 H, 4s, ArH); *m/e* 413 (M^+) (Found: C, 66.8; H, 6.95; N, 3.4. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.9; N, 3.4%).

(b) N-(2-*Ethyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (21).—A solution of the foregoing carbinol (17) (40 mg) in methanol (300 ml) containing concentrated hydrochloric acid (3 drops) was shaken with hydrogen for 15 h in the presence of Pd–C (10%; 40 mg) catalyst. The catalyst was then filtered off, solvent removed *in vacuo*, and the residue treated with water (50 ml). The aqueous solution was neutralised with aqueous sodium hydrogen carbonate and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving a solid which was crystallised from ether–hexane to yield the *isoquinoline* (21), m.p. 113—115°; $\lambda_{max.}$(EtOH) 230 (sh) and 286 nm (log ε 4.11 and 3.90); δ($CDCl_3$) 1.17 (3 H, t, *J* 7 Hz, CH_2Me), 2.70 (2 H, q, *J* 7 Hz, CH_2Me), 2.75 (4 H, s), 3.57br (4 H, s), 3.80 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.90 (2 H, s, OCH_2O), 6.50 (1 H, s), 6.60 (1 H, s), 6.70 (1 H, s), and 6.95 (1 H, s) (Found: C, 70.7; H, 7.4; N, 4.4. $C_{21}H_{25}NO_4$ requires C, 71.0; H, 7.1; N, 3.9%).

Synthesis of N-(2-*Ethyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (21).—α-(3,4-Methylenedioxyphenyl)ethyl alcohol (34 g), prepared according to the method of Klages,[9] was mixed with methanol (100 ml) and concentrated hydrochloric acid (2 ml) and shaken with hydrogen at 50 lb in^{-2} at room temperature for 5 h in the presence of Pd–C (10%; 3.5 g) catalyst. The catalyst was then filtered off, the filtrate was neutralised with sodium hydrogen carbonate, and the solvent was removed *in vacuo*. The residue was taken up in ether, dried (Na_2SO_4), and evaporated. The residue was distilled to give 3,4-methylenedioxyethylbenzene as an oil (18.2 g), b.p. 60° at 0.3 mmHg; δ($CDCl_3$) 1.33 (3 H, t, *J* 7 Hz, CH_2Me), 2.50 (2 H, q, *J* 7 Hz, CH_2Me), 5.75 (2 H, s, OCH_2O), and 6.65 (3 H, ArH).

The foregoing ethylbenzene (5 g) was treated with a cooled solution of concentrated hydrochloric acid (20 ml) and formalin (37%; 4 ml). Hydrogen chloride was passed through the well stirred mixture at 0° for 5 h and the solution was stirred at 0° for an additional 10 h. It was then treated with crushed ice and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated to leave the chloromethylethylbenzene (18) as an oil. A mixture of this compound (1.4 g), 3,4-dihydro-6,7-dimethoxyisoquinoline [10] (0.95 g), and freshly powdered potassium iodide (0.9 g) in dry benzene (25 ml) was heated under reflux overnight. Solvent was decanted off and the residue was treated with potassium iodide (1 g) in water (4 ml), heated on a water-bath, cooled, and the water was decanted off. A solution of the solid residue (0.8 g) in methanol (50 ml) was treated with sodium borohydride (0.6 g). After *ca.* 30 min solvent was removed *in vacuo*, and the residue was treated with water (10 ml) and extracted with methylene chloride. Removal of solvent after drying yielded an oil which later solidified. It was crystallised from ether (100 mg), m.p. 113—115°, identical with the product (21) obtained on degradation of (16a).

Degradation of 5,6,7,8,13,14a-*Hexahydro*-13-*methyl*-2,3:10,11-*bis*(*methylenedioxy*)*isoquino*[1,2-c][2,4]*benzoxazepine* (27a).—To a suspension of (27a) (200 mg) in methanol (50 ml) was added sodium borohydride (200 mg) in portions. The mixture was left at room temperature for 30 min and then evaporated *in vacuo*. The residue was treated with water (30 ml) and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a gum of the hydroxy-compound analogous to (17). A solution of this compound (50 mg)

in methanol (300 ml) containing concentrated hydrochloric acid (3 drops) was shaken with hydrogen for 15 h in the presence of Pd–C (10%; 150 mg) catalyst. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was treated with water (50 ml), neutralised with sodium hydrogen carbonate, and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a solid, which was crystallised from ether–hexane. This compound, m.p. 76°, was found to be identical (m.p., mixed m.p., t.l.c., and i.r.) with *N*-(2-ethyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline described in the next section.

N-(2-*Ethyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline*.—This compound was prepared by a procedure identical to that described for compound (21), from the benzyl chloride (18) and 3,4-dihydro-6,7-methylenedioxyisoquinoline,[11] m.p. 76° (from ether); $\lambda_{max.}$(EtOH) 205, 229 (sh), and 290 nm (log ε 4.38, 4.14, and 4.14); δ($CDCl_3$) 1.19 (3 H, t, *J* 8 Hz, CH_2Me), 2.70 (2 H, q, *J* 8 Hz, CH_2Me), 2.75 (4 H, s), 3.58 (4 H, s), 5.88 and 5.92 (4 H, 2s, 2 × OCH_2O), and 6.50, 6.58, 6.72, and 6.95 (4 H, 4s, ArH); *m/e* 339 (M^+) (Found: C, 70.6; H, 6.5; N, 4.4. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

Resolution of 1-(2-*Bromo*-α-*methyl*-4,5-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (26a).—A mixture of the tetrahydroisoquinoline (26a) (8 g) in dry chloroform (150 ml) and (−)-di-*O*-*p*-toluoyltartaric acid (8.2 g) in dry chloroform (150 ml), was evaporated to dryness under reduced pressure. The residue was crystallised (× 9) from absolute methanol to give white cubic crystals (3 g), m.p. 156—158° (Found: C, 66.75; H, 4.4; N, 1.8. $C_{39}H_{34}BrO_{11}N$ requires C, 66.35; H, 4.4; N, 1.8%), a solution of which in chloroform was washed with dilute aqueous ammonia and then with water, dried (Na_2SO_4), and evaporated to leave a gum which could not be crystallised. This resolved base had identical spectral and analytical data as (26a).

We thank the C.S.I.R. (New Delhi) for Fellowships (both to S. N. and H. S.), the Government of Tamil Nadu, for deputation to do research (R. R.), Professors T. R. Govindachari and M. Shamma for interest, Drs. R. S. Grewal and Selvavinayakam and staff, CIBA-Geigy Research Centre, for analytical and spectral data, and Professor D. Rogers and Dr. A. Quick, Imperial College, London, for the *X*-ray crystallographic studies.

[7/1374 *Received, 4th August,* 1977]

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